



SMAD3 gene

SMAD family member 3

Normal Function

The *SMAD3* gene provides instructions for making a protein involved in transmitting chemical signals from the cell surface to the nucleus. This signaling pathway, called the transforming growth factor-beta (TGF- β) pathway, allows the environment outside the cell to affect cell function, including how the cell produces other proteins. The signaling process begins when a TGF- β protein attaches (binds) to a receptor on the cell surface, which activates a group of related SMAD proteins (including the SMAD3 protein). These SMAD proteins combine to form a protein complex, which then moves to the cell nucleus. In the nucleus, the SMAD protein complex binds to specific areas of DNA to control the activity of particular genes. Through the TGF- β signaling pathway, the SMAD3 protein also influences many aspects of cellular processes, including cell growth and division (proliferation), cell movement (migration), and controlled cell death (apoptosis).

Health Conditions Related to Genetic Changes

familial thoracic aortic aneurysm and dissection

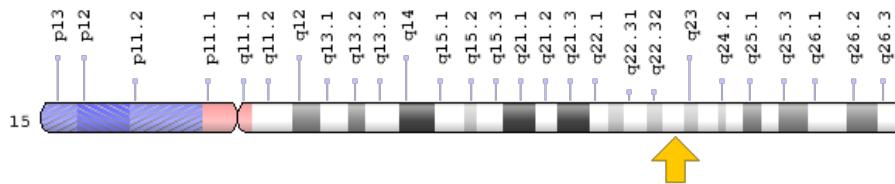
Loeys-Dietz syndrome

At least 35 mutations in the *SMAD3* gene have been found to cause Loeys-Dietz syndrome type III. This disorder affects connective tissue, which gives structure and support to blood vessels, the skeleton, and many other parts of the body. Loeys-Dietz syndrome type III is characterized by abnormal blood vessels, skeletal and joint deformities, and skin abnormalities. Some of the mutations that cause this disorder insert or delete small amounts of genetic material in the *SMAD3* gene, while other mutations result in a change to single protein building blocks (amino acids) in the SMAD3 protein. These mutations lead to the production of a nonfunctional SMAD3 protein. Despite a reduction in SMAD3 function, the TGF- β pathway is overactive. Researchers speculate that the activity of other proteins in this signaling pathway is increased to compensate for the lack of SMAD3 activity; however, the exact mechanism responsible for the increase in signaling is unclear. The overactive signaling pathway leads to dysregulated cell proliferation and gene activation, specifically affecting blood vessel, cartilage, and skin development. These changes lead to the abnormalities typical of Loeys-Dietz syndrome type III.

Chromosomal Location

Cytogenetic Location: 15q22.33, which is the long (q) arm of chromosome 15 at position 22.33

Molecular Location: base pairs 67,065,698 to 67,195,195 on chromosome 15 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- hMAD-3
- hSMAD3
- JV15-2
- MAD homolog 3
- MAD, mothers against decapentaplegic homolog 3
- mad3
- MADH3
- mothers against decapentaplegic homolog 3
- SMAD, mothers against DPP homolog 3
- SMAD3_HUMAN

Additional Information & Resources

Educational Resources

- Developmental Biology (sixth edition, 2000): The Smad pathway activated by TGF- β superfamily ligands
<https://www.ncbi.nlm.nih.gov/books/NBK10043/figure/A1057/>

GeneReviews

- Heritable Thoracic Aortic Disease Overview
<https://www.ncbi.nlm.nih.gov/books/NBK1120>
- Loeys-Dietz Syndrome
<https://www.ncbi.nlm.nih.gov/books/NBK1133>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28SMAD3%5BTI%5D%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1080+days%22%5Bdp%5D>

OMIM

- MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 3
<http://omim.org/entry/603109>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Genes/GC_SMAD3.html
- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=SMAD3%5Bgene%5D>
- HGNC Gene Family: SMAD family
<http://www.genenames.org/cgi-bin/genefamilies/set/750>
- HGNC Gene Symbol Report
http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=6769
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/4088>
- UniProt
<http://www.uniprot.org/uniprot/P84022>

Sources for This Summary

- Liu L, Liu X, Ren X, Tian Y, Chen Z, Xu X, Du Y, Jiang C, Fang Y, Liu Z, Fan B, Zhang Q, Jin G, Yang X, Zhang X. Smad2 and Smad3 have differential sensitivity in relaying TGF β signaling and inversely regulate early lineage specification. *Sci Rep.* 2016 Feb 24;6:21602. doi: 10.1038/srep21602.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/26905010>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4764856/>
- OMIM: MOTHERS AGAINST DECAPENTAPLEGIC, DROSOPHILA, HOMOLOG OF, 3
<http://omim.org/entry/603109>
- Regaldo ES, Guo DC, Villamizar C, Avidan N, Gilchrist D, McGillivray B, Clarke L, Bernier F, Santos-Cortez RL, Leal SM, Bertoli-Avella AM, Shendure J, Rieder MJ, Nickerson DA; NHLBI GO Exome Sequencing Project, Milewicz DM. Exome sequencing identifies SMAD3 mutations as a cause of familial thoracic aortic aneurysm and dissection with intracranial and other arterial aneurysms. *Circ Res.* 2011 Sep 2;109(6):680-6. doi: 10.1161/CIRCRESAHA.111.248161. Epub 2011 Jul 21.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21778426>
Free article on PubMed Central: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4115811/>
- Wischmeijer A, Van Laer L, Tortora G, Bolar NA, Van Camp G, Fransen E, Peeters N, di Bartolomeo R, Pacini D, Gargiulo G, Turci S, Bonvicini M, Mariucci E, Lovato L, Brusori S, Ritelli M, Colombo M, Garavelli L, Seri M, Loeys BL. Thoracic aortic aneurysm in infancy in aneurysms-osteoarthritis syndrome due to a novel SMAD3 mutation: further delineation of the phenotype. *Am J Med Genet A.* 2013 May;161A(5):1028-35. doi: 10.1002/ajmg.a.35852. Epub 2013 Mar 29.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/23554019>
- van de Laar IM, Oldenburg RA, Pals G, Roos-Hesselink JW, de Graaf BM, Verhagen JM, Hoedemaekers YM, Willemsen R, Severijnen LA, Venselaar H, Vriend G, Pattynama PM, Collée M, Majoor-Krakauer D, Poldermans D, Frohn-Mulder IM, Micha D, Timmermans J, Hilhorst-Hofstee Y, Bierma-Zeinstra SM, Willems PJ, Kros JM, Oei EH, Oostra BA, Wessels MW, Bertoli-Avella AM. Mutations in SMAD3 cause a syndromic form of aortic aneurysms and dissections with early-onset osteoarthritis. *Nat Genet.* 2011 Feb;43(2):121-6. doi: 10.1038/ng.744. Epub 2011 Jan 9.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/21217753>
- van de Laar IM, van der Linde D, Oei EH, Bos PK, Bessems JH, Bierma-Zeinstra SM, van Meer BL, Pals G, Oldenburg RA, Bekkers JA, Moelker A, de Graaf BM, Matyas G, Frohn-Mulder IM, Timmermans J, Hilhorst-Hofstee Y, Cobben JM, Bruggenwirth HT, van Laer L, Loeys B, De Backer J, Coucke PJ, Dietz HC, Willems PJ, Oostra BA, De Paepe A, Roos-Hesselink JW, Bertoli-Avella AM, Wessels MW. Phenotypic spectrum of the SMAD3-related aneurysms-osteoarthritis syndrome. *J Med Genet.* 2012 Jan;49(1):47-57. doi: 10.1136/jmedgenet-2011-100382.
Citation on PubMed: <https://www.ncbi.nlm.nih.gov/pubmed/22167769>

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